

Expression and Treatment of Pain-Depressed Behavior in Male ICR Mice

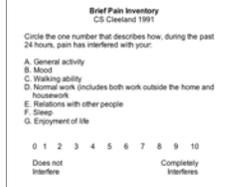
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INTRODUCTION

- Pain-related depression of behavior is a clinically-relevant treatment target.



- Preclinical pain-studies have traditionally relied on examination of pain-stimulated behaviors bearing little resemblance to clinically-relevant consequences of pain.
- This study uses a novel assay of mouse nesting behavior to examine the expression of pain-related depression of behavior, and the potential of drugs to block pain-related depression of behavior.

METHODS

Subjects

- Adult male ICR mice (Harlan), 25-30 g upon arrival in the laboratory
- Individually housed in plastic cages with corncob bedding, and one 5 x 5 cm cotton "nestlet" (Fig 1A)
- Ad libitum access to food (Teklad LM-485 Rodent Chow, Harlan) and water

Behavioral Procedures

- Cages were placed on a lab bench for a 10-min acclimation period
- Treatments were administered by removing the mouse from its cage, administering the treatment, and transferring the mouse to a holding cage
- During pretreatment intervals, the home cage was prepared with six pieces of nesting material evenly distributed into six zones of the cage (Fig 1B&C)
- After expiration of the pretreatment intervals, each mouse was returned to the home cage, and nesting behavior was observed for 100 minutes.
- Nesting was operationally defined as the number of zones cleared of nesting material (Min score = 0; Max score = 5; e.g. Fig 1C&D).

Pharmacological Procedures

- 30-min prior to nesting sessions, intraperitoneal *treatment* injections were administered (see Drugs).
- 5-min prior to nesting sessions, the *noxious stimulus* (intraperitoneal injection of 0.56% lactic acid) was administered.

Drugs

- Ketorprofen – nonsteroidal anti-inflammatory drug (NSAID)
- Citalopram – serotonin-selective monoamine uptake inhibitor
- Nisoxetine – norepinephrine-selective monoamine uptake inhibitor
- Milnacipran – serotonin/norepinephrin monoamine uptake inhibitor

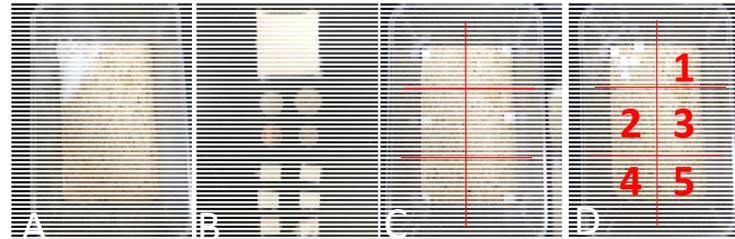


Figure 1
 A – Photograph of male ICR mouse and nest constructed under normal housing conditions
 B – Raw nesting material (top) and six pieces of material cut for use in experiments (bottom)
 C – Nesting material distributed in six zones of cage floor at beginning of nesting session (i.e. 0 zones cleared)
 D – Nesting material consolidated into one zone (i.e. 5 zones cleared)

RESULTS

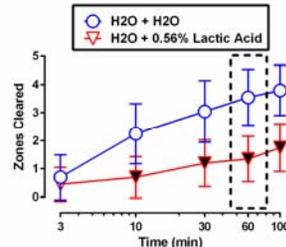


Figure 2. 0.56% Lactic Acid significantly depressed nesting behavior. Symbols show mean zones cleared \pm SD. Filled symbols indicate significant difference from H2O+H2O control (2-way ANOVA; Treatment X Time)

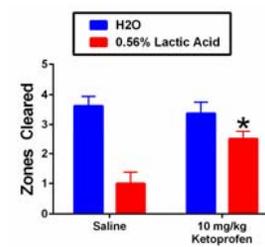


Figure 3. Ketorprofen (10mg/kg) blocked acid-induced depression of nesting. Bars show mean zones cleared \pm SD. Asterisk indicates significant difference from H2O + Acid (2-way ANOVA; Drug X Noxious Stimulus)

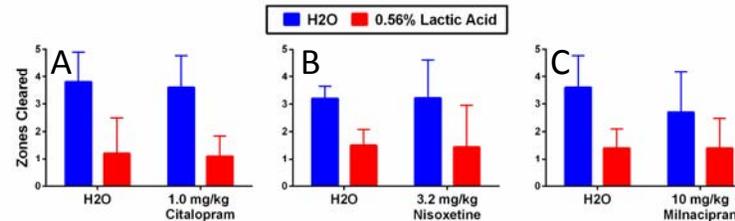


Figure 4. Preliminary data showing effects of A) citalopram, B) nisoxetine, and C) milnacipran on acid-induced depression of nesting behavior (mean zones cleared \pm SD) at the 60-min time point.

DISCUSSION

- Recent findings suggest that research examining pain-related behavioral dysfunction or pain-related depression of behavior may complement traditional reflexive assays of pain-stimulated behavior.
- Rodent behaviors sensitive to depression by noxious stimuli include wheel-running, feeding, and operant behavior.
- Mouse nesting behavior is an innate, stable, behavior that can be studied experimentally
- Nesting is sensitive to physiologically-relevant noxious stimuli
- Noxious stimulus-induced (pain-related) depression of nesting is blocked by a clinically relevant analgesic (ketorprofen)
- These results support the utility of this assay for research on novel pharmacological approaches to the treatment of pain-related depression of behavior
- Future studies include examination of effects of monoamine uptake inhibitors with varying selectivity for inhibition of the uptake of serotonin, norepinephrine, and dopamine.

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